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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/351,617	07/12/99	MEHTA V	15966-518-(C

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1627	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/351,617	Applicant(s) Mehta et al
	Examiner P. Ponnaluri	Group Art Unit 1627

☒ Responsive to communication(s) filed on *Aug 3, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 6, 12-24, 26, 27, and 31* is/are pending in the application.

Of the above, claim(s) *21 and 22* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 6, 12-20, 23, 24, 26, 27, and 31* is/are rejected.

☒ Claim(s) *27* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-27, and 31 in Paper No. 7, filed on 3/27/00 is acknowledged.

2. Applicant's election of species without traverse "combinatorial library of small organic molecules" (claim 23) (in applicants response it was cited as claim 22, which has been considered as a typo, since claim 22 recites combinatorial library of polypeptides), in Paper No. 9, filed on 8/3/00 is acknowledged.

3. The species election requirement of the sample containing environment, and the cells set forth in the previous office action has been withdrawn in view of applicants cancellation of dependent claims 2-5 and claims 7-11.

4. Applicant's traversal of species election of reporter gene (claim 25) in Paper No. 9, filed on 8/3/00 is acknowledged. The traversal is on the ground(s) that claim 25 is a Markush type claim listing several genes commonly used as alternative reporter genes; and the Biosupply Net Source Book lists reporter genes commercially available; and it would be obvious to a person of skilled in the art that any one of the species may be substituted as a reporter gene. This is not found persuasive because the (Markush-type) reporter genes recited in claim 25 are all functionally and structurally are different from each other and the selection of the reporter gene depends on several factors of the assay methods and also would require additional reagents to detect them.

Applicants argue that claim 25 recites few members of the Markush group, which are closely related and share a common utility. Applicants arguments have been considered but are not persuasive, because the even though the members of the Markush group of reporter genes share a common utility, the functional and structural properties are not the same. Applicants argue that the search for closely related members of the Markush group is not burden to search. Applicants arguments have been considered but are not persuasive because the search for each member of the Markush members of claim 25 is not the same, and the prior art reference for one member of the Markush group of claim 25 would not render obvious of other members. For the reasons of the above the species election has been maintained.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 21-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected species election. Election was made **without** traverse in Paper No. 9, filed on 8/3/00.

6. Claims 2-5, 7-11, 25, and 28-30 have been canceled by the amendment filed on 8/3/00, paper number 9.

7. Claims 1, 6, 12-24, 26-27 and 31 are currently pending in this application.

8. Claims 1, 6, 12-20, 23-24, 26-27 and 31 are currently being examined in this application.

Priority

9. This application claims priority to provisional application 60/094,450 filed on 7/28/98.

Oath/Declaration

10. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The address of Inventor Vimal D. Mehta has been altered without initials.

Drawings

11. Applicant is invited to notice that boxes 5, 10 and 12 were checked by the draftsman. If applicants renumber the figures, applicant is encouraged to amend the specification so that the description of renumbered figures corresponds to the renumbered figures.

Specification

12. The use of the trademark SIGMA (in page 10, line 14) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

14. Claim 27 is objected to because of the following informalities: in line 3, of claim 27, after ligand B "a period" (.) is present which may be a typo. Appropriate correction is required.

Claim Rejections - 35 U.S.C § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1, 6, 12-20, 23-24, 26-27 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the hybrid molecule" in step (b). There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites 'wherein the environment of step (b) is selected from **a group** consisting of insect cells, yeast cells, mammalian cell and their lysates', which is a improper Markush format. Applicants are requested to amend the claim as "wherein the environment of step (b) is selected

from **the group** consisting of insect cells, yeast cells, mammalian cell , insect cell lysate, yeast cell lysate and mammalian cell lysate".

Claim 14 recites the limitation "the DNA fragments" in line 1. There is insufficient antecedent basis for this limitation in the claim or in claim 13.

Claim 16 recites the limitation "the cDNA library" . There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "the small molecule contaminant" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 18 recites, the phrase "*e.g.*, aspirin-cyclooxygenase" in parenthesis, which renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 18 is vague and indefinite by reciting 'wherein the ligand A or B of step (a) is a mechanism based irreversible enzyme in activator'. Applicants are requested to clarify the meaning of ' ligand A or B is a mechanism of irreversible enzyme in activator.

Claim 26 recites the limitation "the cell component" . There is insufficient antecedent basis for this limitation in the claim or in claim 1.

Claim 27 recites ' wherein the steps (b)- (e) of the method are repeated using an expression vector .....in the presence of preparation random small molecules for competitive binding with the hybrid molecule'. Clarification is requested what does applicant mean by in the presence of

preparation of random small molecules for competitive binding. Does applicants mean that the steps (b) - (e) of the method are repeated in during the preparation of random small molecule.

Claim 31 recites the limitations "the binding protein" in step (b); "the first and second target proteins" in step (d); "the hybrid proteins" in step (e); and "the hybrid ligands" in step (e). There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 U.S.C § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. Claims 1, 6, 12, 17, 19, 20, and 23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Licitra et al (Proc. Natl. Acad. Sci. USA., vol. 93, pp. 12817-12821, November 1996) (cited by applicants in the PTO-1449, filed on 12/9/99).

The instant claims are drawn to a method and a kit of reagents (claim 31) for identifying a cellular component to which a small molecule is capable of binding, comprising: providing a hybrid ligand having ligands A and B; wherein ligand A forms a covalent bond with a predetermined target, and ligand B is small molecule; introducing the hybrid ligand into a sample

containing: (I) a first expression vector encoding a first hybrid protein comprising the target of ligand A and a first transcriptional module, (ii) a second expression vector encoding a second hybrid protein comprising the a random DNA fragment encoding a polypeptide and a second transcriptional module, (iii) a third vector including a reporter gene, and the reporter gene is expressed when the first and second proteins are in proximity; permitting the hybrid molecule to bind covalently the first hybrid protein through the ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene; identifying the samples expressing the reporter gene; and characterizing the second hybrid protein in the samples so as to determine the cellular component to which small molecule has a binding affinity.

Licitra et al disclose a three-hybrid system (method) for detecting small ligand-protein receptor interactions in vivo (see the abstract). The reference discloses that the method comprises a synthetic 'bait' hybrid ligand (hybrid ligand of the instant claims) comprising dexamethasone (refers to ligand A of the instant claims) and FK 506 (refers to ligand B of the instant claims; and instant claim 19 (small molecule has a known function)) (see the abstract and diagram 2, in page 12819). The reference discloses that the hybrid ligand was introduced to a yeast strain (EGY48) expressing fusion proteins (refers to hybrid proteins of the instant claims) 'hook fusion protein' and 'fish fusion protein', wherein the hook fusion protein has a hormone binding domain of rat glucocorticoid receptor (receptor for ligand A) fused to LexA DNA binding domain (refers to transcriptional module of the instant claims and instant claim 12); and the fish fusion protein has FKBP12 (receptor for ligand B) fused to a transcriptional activation domain of a transcriptional

factor (refers to second transcriptional module of the instant claims and instant claim 12). The 'fish', and 'hook' proteins (fusion proteins) and bait hybrid ligand form the three hybrid molecules. The reference discloses that when the ligand A binds to its receptor fused to a DNA binding domain of the 'hook fusion protein; and ligand B binds to its receptor fused to a transcriptional activation domain of the 'fish fusion protein' the reporter genes are activated allowing for the selection of the yeast cells that harbor the relevant receptors (see page 12819, left column, and also the diagram 2) (refers to steps (b) - (e) of claim 1 of the instant claims). The reference discloses that the disclosed method of three hybrid system has advantages over known biochemical methods for identifying receptors for small ligands , and the method will also be useful for generation of high affinity binding proteins to small ligands such as environmentally hazardous compounds or drugs. The reference also discloses that the three hybrid system can also be applied to screen for novel ligands for a given receptor both in yeast and in mammalian cells in vivo (refers to instant claim 6). The reference discloses that with the availability of synthetic combinatorial libraries of small organic molecules, the system offers highly efficient way to identifying such ligands (see page 12820, right column) (refers to instant claims 20 and 23). The reference also discloses that in the case of receptor with no known ligand it is conceivable that a hybrid combinatorial library of covalently linked to a known ligand such as dexamethasone can be screened to discover new lead compounds for drug development. The reference discloses that the DNA fragment encoding a polypeptide of the second expression vector is from a cDNA library (i.e, see figure 4, and page 12820, left column) (refers to random DNA fragment of the instant

claims). The reference discloses that the second vectors (fish vectors) from the colonies which were completely inhibited by the FK506 (ligand B) were retrieved and sequenced the cDNA inserts (refers to step (e) of the instant claims). Thus, the reference clearly anticipates the claimed invention.

19. Claims 1, 6, 12-17, 19-20, 23-24, 26-27 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,928,868 (Liu et al) (cited by applicants in the PTO-1449, filed on 12/9/99).

Liu et al disclose a three hybrid screening assay. Liu et al disclose methods and kit for characterizing small molecules from a library of small molecules or alternatively identifying a protein targets to which known small molecules bind (see abstract). The reference method includes forming a hybrid ligand in which at least one molecule is a small molecule. (See the abstract). The hybrid ligand is introduced into cells that in turn contain a first and second expression vector containing DNA for expressing a hybrid protein and a transcriptional module, and a third vector with a reporter gene, expression of which is conditioned on the proximity of the first and second hybrid proteins (see abstract). The reference discloses that the three hybrid system involves the formation of a complex between a hybrid ligand and two hybrid proteins in which one component of the complex is unknown, and the unknown component in the assay may be either small molecule contained in the hybrid ligand or one of the hybrid proteins (see column 5, lines 16-21). The reference discloses that the utility of the assay include determining the identity of a target molecule having a binding affinity with a known small molecule where the small

molecule has a pharmacologic activity and the target may be suited for therapeutic intervention in a variety of diseases (see column 5). The reference method discloses that the hybrid ligand comprises a small molecule (refers to ligand B of the instant claims) and a known molecule (refers to ligand A of the instant claims), and the known molecule binds to a known second target (refers to predetermined target; and the covalent bond of the instant claims) (see claim 1, step (a)). The reference discloses that the hybrid ligand is introduced into cell containing a first expression vector containing a DNA encoding a first known target, linked to a coding sequence of a first transcriptional module for expression as first hybrid protein; a second expression vector containing DNA fragment encoding a polypeptide linked to a transcriptional module for expression as a second hybrid protein ; and a third vector containing a reporter gene (refers to the step (b); and the cells refer to the environment of the instant claims) (see i.e., claims 1 and 17, step (b)). The reference discloses that the hybrid ligand binds to the first hybrid protein and the second hybrid protein so as to activate the expression of the reporter gene (refers to step (c) of the instant claims (i.e., see claim 1 , step (c)); and claim 17, steps (d) and (e) of the reference method refers to steps (d) and (e) of the instant claims. The reference discloses that the random fragment of second vector are selected from genomic DNA, cDNA, synthetic DNA or from a plurality of libraries (i.e., see claims 20-21) (refers to instant claims 14- 15). The reference discloses that the cDNA is derived from an immune cell, or from an immune cell capable of producing an immune response to ligand B (refers to small molecule contaminant) (i.e., see claims 22-23) (refers to instant claims 16-17). The reference discloses that the ligand B has a known

biological function (i.e., see claim 24) (refers to instant claim 19). The reference discloses that the cells are mammalian cells (see i.e., claims 6, 29) or yeast cells (see i.e., claims 5, 28), or the lysates (see i.e., claim 4) (refers to instant claim 6 of the instant claims). The reference discloses that the transcriptional modules are selected from DNA binding protein and a trascriptional activator (i.e., see claim 10), and the small molecule is obtained from a combinatorial library of small organic molecules (see i.e., claims 12-13) (refers to instant claims 20 and 23). The reference discloses that the small molecule is an environmental contaminant (see claim 14) (refers to claim 24 of the instant claims). The reference method further disclose that the method steps (b) to (e) are repeated in the presence of random small molecules for the competitive binding with the hybrid ligand (see i.e, claim 16) (refers to instant claim 27). The reference discloses that a random DNA sequences of a size that is capable of encoding undetermined target protein may be inserted in the second expression vector where the random DNA sequences are derived from a genomic DNA library, cDNA library or synthetically generated library from eukaryotic cells, prokaryotic cells, viruses or formed by an automated DNA synthesizer (i.e., see column 8, lines 2-8). The reference discloses a kit for detecting interactions between the pharmacologically relevant small molecules and proteins comprising: (a) a hybrid ligand; (b) a first expression vector; (c) a second expression vector; (d) a third vector; (e) an environment for transcription and translation; and (f) a means for detecting the expression of the reporter gene (see i.e., claim 18) (refers to instant claim 31). The reference clearly anticipates the claimed invention.

Claim Rejections - 35 U.S.C § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1, 6, 12, 17, 19, 20, 23-24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Licitra et al (Proc. Natl. Acad. Sci. USA, vol. 93, pp 12817-12821, November 1996) (cited by applicants in the PTO-1449, filed on 12/9/99).

Licitra et al has been discussed supra. The claimed invention differs from the prior art teachings by reciting a kit (claim 31) for detecting interaction between pharmaceuticologically relevant small molecules and proteins. Licitra et al teach three hybrid system comprising a hybrid molecule comprising ligand A and ligand B; hook fusion protein (hybrid protein) comprising a receptor for ligand A and a first transcriptional module; a fish fusion protein comprising a receptor

for ligand B and a transactivation domain ; reporter gene; yeast cell (environment for transcription and translation). The reference do not teach a kit comprising all the reagents. However, based on the disclosure of the reference, it would be obvious to one skilled in the art at the time of the invention to formulate and dispense the reagents used in the three hybrid method in a kit for ease of use.

22. Claims 1, 6, 12-20, 23-24, 26-27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18317 (Crabtree et al) in view of US Patent 5,610,015 (Wickens et al) (cited by applicants in the PTO-1449, filed on 12/9/99).

Crabtree et al teach a three hybrid assay system comprising introducing a hybrid ligand having two different ligands which are small molecules into a sample containing (I) a first expression vector encoding a first hybrid protein comprising the target of one of the ligands of the hybrid ligand and a transcriptional module, (ii) a second expression vector encoding a second hybrid protein comprising the target of the other ligand of the hybrid ligand and a second transcriptional module, and a (iii) vector including a reporter gene such that the reporter gene is expressed when the first and second ligands of the hybrid ligand bind to their perspective target of the first and second vectors (see pages 5, 6, 30-33 and figure 14).

The claimed invention differs from the prior art teachings by reciting the second vector comprises a random DNA fragment derived from cDNA library. Crabtree et al do not teach that the DNA fragment is random. However, Wickens et al disclose a similar hybrid system. Wickens et al disclose that the hybrid ligand comprises two different RNA ligands which bind to proteins.

Wickens et al disclose that the assay system is analogous to that of Crabtree et al, and also may incorporate random components derived from a library in order to identify new binding members. Wickens et al disclose kits useful in the three hybrid assay system.

Thus the person of ordinary skill in the art would have been motivated to modify the method of Crabtree et al by including the random fragments in the second vector, because Wickens et al teach that the use of random fragments have advantageous for screening for useful binding ligands/proteins. It would have been obvious to person of ordinary skill in the art at the time the invention was made to use random fragments in the assay method taught by Crabtree et al because Wickens et al use them in analogous three hybrid assay, and also it would have been obvious to a person of ordinary skill in the art to make the claimed kit for ease of use.

23. No claims are allowed.

24. The references C2, C7 and C12 cited in PTO 1449, filed on 9/2/99 have not been considered by the examiner because the page numbers and author names and the publication information are not provided by the applicants, and these references are kept in the application file.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner can normally be reached on Monday to Thursday from 6.30 AM to 4.00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venakt, Ph.D., can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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